AWARD NUMBER: W81XWH-14-1-0568

TITLE: rTMS: A Treatment to Restore Function After Severe TBI

PRINCIPAL INVESTIGATOR: Theresa Pape, DrPH

CONTRACTING ORGANIZATION:

Chicago Association for Research and Education in Science
Hines, IL 60141

REPORT DATE: October 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2016	Annual	30 Sept 2015 – 29 Sept 2016

4. TITLE AND SUBTITLE

rTMS: A Treatment to Restore Function After Severe TBI

5a. CONTRACT NUMBER

5b. GRANT NUMBER W81XWH-14-1-0568

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Dr. Theresa Pape

E-Mail: Theresa.Pape@va.gov

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Chicago Association for Research and Education
5000 South 5th Avenue
Bldg. One C347
Hines, IL 60141

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This study is a ***double blind randomized placebo-controlled clinical trial using repeated measures***. The ***objective*** is to improve recovery of functional skills for persons living in states of seriously impaired consciousness 3 to 12 months after severe TBI. This will be achieved by determining the neurobehavioral and neural effects of repetitive transcranial magnetic stimulation (rTMS), which is a non-invasive technique to stimulate the brain. The evidence of therapeutic efficacy from the literature in non-TBI related neurologic populations combined with our preliminary findings with severe TBI, indicate that rTMS merits investigation as a neurotherapeutic for severe TBI and that the proposed repetitive TMS protocol should be examined to determine effectiveness in inducing structural and functional neural plasticity and improving neurobehavioral recovery after severe TBI. ***Specific Aims***: Aim I will determine presence, direction and sustainability of rTMS-induced neurobehavioral effects measured with the Disability Rating Scale. Aim II will determine the presence, direction and sustainability of rTMS-induced changes in functional neural activation and whether or not these changes correlate with improving neurobehavioral function. Aim III will examine the effect of rTMS on white fiber tracts and whether or not the rTMS-related effects correlate with improving neurobehavioral function. Aim IV addresses the need to confirm rTMS safety for severe TBI.

15. SUBJECT TERMS

Disability Rating Scale (DRS), Neurobehavioral, Repetitive Transcranial Magnetic Stimulation (rTMS), Traumatic Brain Injury (TBI), Vegetative (VS), Minimally Conscious (MCS)

16. SECURITY CLASSIFICATION OF: Unclassified			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
	Unclassified	Unclassified	Unclassified		19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

1. **INTRODUCTION:** The rationale, based on published evidence and pilot data from three subjects, indicate that repetitive Transcranial Magnetic Stimulation (rTMS) holds promise as a treatment for severe Traumatic Brain Injury (TBI). TBI alters the lives of the patient, their family and society. Severe TBI is particularly devastating with some survivors recovering full consciousness swiftly while others remain in states of seriously impaired consciousness (SIC). Both recovery trajectories involve complex and potentially chronic cognitive and physical impairments. Evidence that cortical processing can occur even while unconscious and evidence of late recoveries continues to accumulate suggesting that SIC is a modifiable condition. Advanced medical care saves and sustains the lives of persons incurring severe TBI and there is a growing body of evidence indicating that this devastating injury is modifiable but there are few to no treatments that induce or accelerate functional and adaptive recovery for survivors of severe TBI. Optimal functional recovery after severe TBI, without targeted treatments, is unlikely. To address the need for targeted treatments that induce functional and structural changes in the brain, ultimately improving neurobehavioral functioning, we propose examining the therapeutic effectiveness of rTMS. The objective is to improve functional recovery for persons remaining in vegetative (VS) and minimally conscious (MCS) states 3 to 12 months after severe TBI. The approach is to determine the neurobehavioral effect of rTMS, the relationship between neurobehavioral changes and net neural effects, and to identify and define the neural mechanisms related to neurobehavioral improvements by providing 30 active or placebo rTMS sessions. The Disability Rating Scale (DRS) will be used at four time points to measure neurobehavioral recovery slopes. Net neural effects will be measured at three time points using fcMRI, resting state EEG (EEG-Rest), a language fMRI task and changes in EEG power spectrum when listening to a semantic processing task (EEG-Task). We will examine changes in structural integrity of fiber tracts using DTI. Measures are collected prior to, during, after and at follow up from active and placebo rTMS treatments.

2. **KEYWORDS:**

Disability Rating Scale (DRS)
Neurobehavioral
Repetitive Transcranial Magnetic Stimulation (rTMS)
Traumatic Brain Injury (TBI)
Vegetative (VS)
Minimally Conscious (MCS)

3. **ACCOMPLISHMENTS:**

What were the major goals of the project?

Major Goal 1: Regulatory Requirements (Months 1-4)
Milestones: Local IRB approval and HRPO/ORP approval; **90% completed**
Major Goal 2: Coordinate Study Staff and Logistics for Study (Months 1-4)
Subtask 2a: Hiring and Training of Study Staff
Milestones: Study staff hired and trained at all 3 study sites; **100% completed**
Subtask 2b: Development of study related materials and finalize logistics

Milestones: All study materials and procedures finalized at all 3 study sites; **100% completed**

Major Goal 3: Participant Recruitment, rTMS Intervention and Follow-up (Months 4-32)
Milestones: All 58 study participants recruited and completion of research participation; **1.7% completed**

Major Goal 4: Data Analysis (Months 5-36); **0% completed**

What was accomplished under these goals?

For Major Goal 1, The FDA approved the last supplement which outlined changes to the placebo coil design on 4/13/16. The Hines IRB approved the amendment on the placebo coil design changes on 6/6/16 and HRPO also approved the changes on 6/17/16. The same amendment was submitted to Northwestern's IRB and the IRB came back with requests for changes in the protocol not related to the placebo coil design. Once the changes are made and the amendment is approved by Northwestern, the approval will be submitted to HRPO. SCVMC's IRB approved the study protocol on 5/6/16. An amendment was submitted to SCVMC for the placebo system and the SCVMC IRB verbally approved for the placebo coil design changes. Once the official approval letter is received, SCVMC's protocol will be sent to HRPO for approval. IRB and FDA approval has been obtained at all research sites for the placebo coil design. SCVMC has obtained IRB approval; we are waiting for one final document to be approved from their IRB before submitting the SCVMC paper work to HRPO. No other IRB updates. We have reported an unanticipated event to the Northwestern IRB with our current participant at Northwestern. The participant developed increased secretions and need for suctioning which was judged by the physician to be related to the weaning off of amantadine for participation in this study. No serious adverse events developed in relation to this occurrence.

For Major Goal 2, all study staff have been hired at all three sites.

For Major Goals 3 and 4, a civilian participant was enrolled at Northwestern and finished the TMS portion of the study on October 27th. This participant's surrogate learned of the trial on clinicaltrials.gov and contacted us. The participant will return to Northwestern Memorial Hospital on November 28 for the final follow-up. During this reporting period we have screened 48 active duty/veterans and civilians of which 9 were eligible and 8 are still being considered. We are currently in communication with 3 civilian participant families who may be interested in screening for eligibility. Formal screening of the civilians has not been initiated yet. There is an active duty patient at Palo Alto that may be eligible for study participation who we are seeking proper approvals through the VA to approach and screen for potential inclusion.

What opportunities for training and professional development has the project provided? Nothing to report.

How were the results disseminated to communities of interest? Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?

During the next quarter we plan to consent 2 participants at the Chicago sites and 2 participants at SCVMC once final HRPO approvals are obtained for the SCVMC site.

4. **IMPACT:** Nothing to report.

5. **CHANGES/PROBLEMS:**

Changes in approach are **not** anticipated at this time.

Problems:

- Brett Blabas, Biomedical Engineer at Hines VA is expected to terminate her employment on November 11th. She has agreed to act as a consultant to ensure a smooth transition while we look to hire a replacement.
- In the next quarter, we may experience difficulty enrolling more than one person per site given bed availability during the holiday season. We are working with each institution to work out a resolution.
- We currently have a piece of equipment used for treatment out for repair. The vendor is working to repair the equipment before another subject is enrolled. In the meantime, we are seeking a substitute so as not to delay treatment.

6. **PRODUCTS:** Nothing to Report

7. **PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS:**

What individuals have worked on the project?

Name: *Brett Blabas, MS*
Project Role: *Biomedical Engineer at Hines VA*
Nearest person month worked: *1*
Contribution to Project: *Ms. Blabas has administered treatment and has performed trouble-shooting on equipment.*

Name: *Ann Guernon, MS, CCC-SLP, CCRC*
Project Role: *Clinical Research Coordinator at Hines VA*
Nearest person month worked: *1.5*
Contribution to Project: *Ms. Guernon has overseen Hines VA and Northwestern IRB amendments as well as SCVMC's initial IRB submission packet. Ms. Guernon has prepared and will continue to prepare all submissions to HRPO and interface with HRPO to address needed amendments. She has also been actively involved in subject recruitment and screening and data collection procedures for the enrolled participant.*

Name: *Theresa Pape, DrPH, MA, CCC-SLP*
Project Role: *PI*
Nearest person month worked: *1*

Contribution to Project: *Dr. Pape has overseen protocol development, staffing at each study site and overall project flow.*

Name: *Elyse Walsh*
Project Role: *Research Clinical Therapist*
Nearest person month worked: *1.5*
Contribution to Project: *Dr. Walsh has administered treatment and neurobehavioral testing for research subject . She has also been actively involved in subject recruitment and screening and data collection procedures for the enrolled participant.*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

The following changes have occurred in the active other support of the PI and key personnel:

Pape, Theresa Louise-Bender

New Support

JW150040 (PI-Pape) 08/16 – 07/20 2.4 Calendar Months
$3,014,625
"Advancing Clinical Outcomes, Biomarkers and Treatments for Severe TBI"
Congressionally Directed Joint Warfighter Medical Research Program
This proposal was submitted to support three projects complementing Dr. Pape's currently funded DoD CDMRP project # W81XWH-14-1-0568. The purpose of Project 1 is to address a series of critical measurement issues that will advance endpoint development for the TBI research community. This will be achieved by leveraging the unique data collection procedures already being implemented as part of currently funded research. The purpose of Project 2 is to identify specific miRNA in peripheral blood and within microparticles altered by the rTMS intervention and that are correlated with the neurobehavioral outcomes as well as neurophysiological outcomes. The purpose of Project 3 is to optimize subject recruitment and support 8 additional bed days per subject for currently funded CDMRP Phase II clinical trial.

No Grant No. (PI-Pape) 04/16-04/17
$10,000
Disabled National Veterans Fondation (DVNF)
Financial Assistance Grant
Deborah Onaderu
Junior Program Officer
Email: donadeu@dvnf.org; Phone #202-737-0522
This funding will support the participation of Veterans and Military personnel in two funded clinical trials. The clinical trials are funded by federal research grants, but there are fiscal barriers that will prohibit severely disabled and vulnerable Veterans and Military personnel from taking advantage of an opportunity to participate in a clinical trial. One of

the clinical trials enrolls patients remaining in states of seriously impaired consciousness after severe TBI and the other trial enrolls patients with mild TBI and PTSD who are experiencing persisting impairments in attention.

Parrish, Todd

New Support

B6500002/B6500003 (Parrish) 01/01/15-09/30/18
0.24 CY
Advocate Health and Hospitals Corporation $23,425
The Parkinson's Progression Markers Initiative (PPMI) – T1 Standardization Sub-study
The goal of this project is to oversee implementation of T1 standardization and ongoing quality control and to work with sites to implement protocol and adjust parameters related to the PPMI T1 standardization sub-study.

Herrold, Amy

New Support

JW150040 (PI-Pape) 08/16 – 07/20 2.4 Calendar Months
$3,014,625
"Advancing Clinical Outcomes, Biomarkers and Treatments for Severe TBI"
Congressionally Directed Joint Warfighter Medical Research Program
This proposal was submitted to support three projects complementing Dr. Pape's currently funded DoD CDMRP project # W81XWH-14-1-0568. The purpose of Project 1 is to address a series of critical measurement issues that will advance endpoint development for the TBI research community. This will be achieved by leveraging the unique data collection procedures already being implemented as part of currently funded research. The purpose of Project 2 is to identify specific miRNA in peripheral blood and within microparticles altered by the rTMS intervention and that are correlated with the neurobehavioral outcomes as well as neurophysiological outcomes. The purpose of Project 3 is to optimize subject recruitment and support 8 additional bed days per subject for currently funded CDMRP Phase II clinical trial.

Kletzel, Sandra

New Support

JW150040 (PI-Pape) 08/16 – 07/20 2.4 Calendar Months
$3,014,625
"Advancing Clinical Outcomes, Biomarkers and Treatments for Severe TBI"
Congressionally Directed Joint Warfighter Medical Research Program
This proposal was submitted to support three projects complementing Dr. Pape's currently funded DoD CDMRP project # W81XWH-14-1-0568. The purpose of Project 1 is to address a series of critical measurement issues that will advance endpoint

development for the TBI research community. This will be achieved by leveraging the unique data collection procedures already being implemented as part of currently funded research. The purpose of Project 2 is to identify specific miRNA in peripheral blood and within microparticles altered by the rTMS intervention and that are correlated with the neurobehavioral outcomes as well as neurophysiological outcomes. The purpose of Project 3 is to optimize subject recruitment and support 8 additional bed days per subject for currently funded CDMRP Phase II clinical trial.

Bhaumik, Dulal

New Support

JW150040 (PI-Pape) 08/16 – 07/20 2.4 Calendar Months
$3,014,625
"Advancing Clinical Outcomes, Biomarkers and Treatments for Severe TBI"
Congressionally Directed Joint Warfighter Medical Research Program

This proposal was submitted to support three projects complementing Dr. Pape's currently funded DoD CDMRP project # W81XWH-14-1-0568. The purpose of Project 1 is to address a series of critical measurement issues that will advance endpoint development for the TBI research community. This will be achieved by leveraging the unique data collection procedures already being implemented as part of currently funded research. The purpose of Project 2 is to identify specific miRNA in peripheral blood and within microparticles altered by the rTMS intervention and that are correlated with the neurobehavioral outcomes as well as neurophysiological outcomes. The purpose of Project 3 is to optimize subject recruitment and support 8 additional bed days per subject for currently funded CDMRP Phase II clinical trial.

Issac, Linda

New Support

JW150040 (PI-Pape) 08/16 – 07/20 2.4 Calendar Months
$3,014,625
"Advancing Clinical Outcomes, Biomarkers and Treatments for Severe TBI"
Congressionally Directed Joint Warfighter Medical Research Program

This proposal was submitted to support three projects complementing Dr. Pape's currently funded DoD CDMRP project # W81XWH-14-1-0568. The purpose of Project 1 is to address a series of critical measurement issues that will advance endpoint development for the TBI research community. This will be achieved by leveraging the unique data collection procedures already being implemented as part of currently funded research. The purpose of Project 2 is to identify specific miRNA in peripheral blood and within microparticles altered by the rTMS intervention and that are correlated with the neurobehavioral outcomes as well as neurophysiological outcomes. The purpose of Project 3 is to optimize subject recruitment and support 8 additional bed days per subject for currently funded CDMRP Phase II clinical trial.

Duong, Thao

New Support

JW150040 (PI-Pape) 08/16 – 07/20 2.4 Calendar Months
$3,014,625
"Advancing Clinical Outcomes, Biomarkers and Treatments for Severe TBI"
Congressionally Directed Joint Warfighter Medical Research Program
This proposal was submitted to support three projects complementing Dr. Pape's currently funded DoD CDMRP project # W81XWH-14-1-0568. The purpose of Project 1 is to address a series of critical measurement issues that will advance endpoint development for the TBI research community. This will be achieved by leveraging the unique data collection procedures already being implemented as part of currently funded research. The purpose of Project 2 is to identify specific miRNA in peripheral blood and within microparticles altered by the rTMS intervention and that are correlated with the neurobehavioral outcomes as well as neurophysiological outcomes. The purpose of Project 3 is to optimize subject recruitment and support 8 additional bed days per subject for currently funded CDMRP Phase II clinical trial.

Trudy Mallinson

New Support

JW150040 (PI-Pape) 08/16 – 07/20 2.4 Calendar Months
$3,014,625
"Advancing Clinical Outcomes, Biomarkers and Treatments for Severe TBI"
Congressionally Directed Joint Warfighter Medical Research Program
This proposal was submitted to support three projects complementing Dr. Pape's currently funded DoD CDMRP project # W81XWH-14-1-0568. The purpose of Project 1 is to address a series of critical measurement issues that will advance endpoint development for the TBI research community. This will be achieved by leveraging the unique data collection procedures already being implemented as part of currently funded research. The purpose of Project 2 is to identify specific miRNA in peripheral blood and within microparticles altered by the rTMS intervention and that are correlated with the neurobehavioral outcomes as well as neurophysiological outcomes. The purpose of Project 3 is to optimize subject recruitment and support 8 additional bed days per subject for currently funded CDMRP Phase II clinical trial.

What other organizations were involved as partners?

Organization Name: Northwestern University
Location of Organization: Chicago, IL, USA
Partner's Contribution to the Project: Collaboration

Organization Name: Santa Clara Valley Medical Center
Location of Organization: San Jose, CA, USA

Partner’s Contribution to the Project: Collaboration

8. **SPECIAL REORTING REQUIREMENTS:** None.
9. **APPENDICES:** None

QUAD CHARTS: See attached Quad Chart.